Complete Summary

GUIDELINE TITLE

Venous thromboembolism.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Venous thromboembolism. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Feb. 92 p. [254 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Hematology

Internal Medicine
Pulmonary Medicine
Radiology
Vascular Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To prevent progression or recurrence of thromboembolic disease
- To reduce the risk of complications from anticoagulation therapy
- To reduce resources and costs used in the diagnosis and treatment of venous thromboembolism (VTE)

TARGET POPULATION

Adult patients age 18 and over with venous thromboembolism (VTE)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation of Deep Vein Thrombosis (DVT)

1. Clinical pretest probability model (protocol) of deep vein thrombosis (DVT), such as the Well's Model
2. D-dimer assays, such as enzyme linked immunoassay (ELISA); rapid ELISA (VIDAS®); and SimpliRED®
3. Venous Doppler ultrasound
4. Serial compression ultrasounds
5. Computed tomography (CT) venography of the iliac and vena cava
6. Contrast venography (proximal, intra-abdominal)
7. Magnetic resonance imaging (MRI)

   Note: Magnetic resonance imaging is considered experimental for the diagnosis of deep vein thrombosis.

Diagnosis/Evaluation of Pulmonary Embolism (PE)

1. Assessment of patient's clinical signs and symptoms, such as dyspnea, pleuritic chest pain, and tachypnea
2. Patient history and physical examination, including risk factor assessment for venous thromboembolism (VTE)

3. Laboratory evaluation, including chest x-ray; arterial blood gasses; and electrocardiogram (ECG)
4. Clinical pretest probability model for predicting probability of pulmonary embolism
5. Echocardiography
6. Ventilation/perfusion (V/Q) scan
7. Helical computed tomography pulmonary angiography
8. Compression ultrasound
9. D-dimer (ELISA or automated luminescence immunoassay [LIA])
10. Serial ultrasound

Treatment/Management for Venous Thromboembolism

1. Anticoagulation with warfarin
2. Low molecular weight heparin (LMWH), such as enoxaparin (Lovenox®), tinzaparin (Innohep®), dalteparin (Fragmin®)
3. Unfractionated heparin (UFH)
4. Heparin alternatives, such as fondaparinux (Arixtra)
5. Baseline and periodic platelet counts during heparin therapy
6. Patient education on the use of anticoagulation
7. Inferior vena cava (IVC) filters
8. Direct thrombin inhibitors such as lepirudin (Refludan®), argatroban (Acova®) and bivalirudin (Angiomax®) for treatment of heparin-induced thrombocytopenia
9. Activated partial prothromboplastin time (aPPT) monitoring during direct thrombin inhibitor therapy
10. Intravenous (IV) thrombolytic therapy
11. Surgical thrombectomy
12. Graded compression stockings

MAJOR OUTCOMES CONSIDERED

- Sensitivity, specificity, positive/negative predictive value, and utility of diagnostic tests
- Patient signs and symptoms
- Patient response to treatment
- Recurrence of thrombosis
- Complications of treatment (e.g., bleeding, heparin-induced thrombocytopenia)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline draft, discussion and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member medical groups during an eight-week period of "Critical Review".

Each of the Institute's participating medical groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating medical groups following general implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group: Second Draft

Following the completion of the "Critical Review" period, the guideline work group meets 1-2 times to review the input received. The original guideline is revised as necessary and a written response is prepared to address each of the suggestions received from medical groups. Two members of the Cardiovascular Steering Committee carefully review the Critical Review input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of two questions: (1) Have the concerns of the medical groups been adequately addressed? (2) Are the medical groups willing and able to implement the guideline? The committee then either approves the guideline for pilot testing as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Medical groups introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occurs throughout the pilot test phase, which usually lasts for three months. Comments and suggestions are solicited in the same manner as used during the "Critical Review" phase.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Cardiovascular Steering Committee reviews the revised guideline and approves it for implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for venous thromboembolism are presented in the form of three algorithms, accompanied by detailed annotations. Algorithms on Deep Vein Thrombosis (DVT) Diagnosis; Pulmonary Embolism (PE) Diagnosis; and Venous Thromboembolism (VTE) Treatment are provided. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) ratings and key conclusion grades (I-III, Not Assignable) are defined at the end of the Major Recommendations field.

Clinical Highlights and Recommendations

1. Confirm diagnosis of deep vein thrombosis (DVT) with imaging study, preferably compression ultrasound. (Annotations #7, 10)
2. A clinical pretest probability assessment should be completed in patients with suspected venous thromboembolism. (Annotations #2, 15)
3. D-dimer can be used as a negative predictor to eliminate need for further testing. (Annotations #4, 11)
4. In patients with a high clinical pretest probability for PE, begin low-molecular-weight heparin (LMWH) without delay. (Annotation #15)
5. Achieve rapid effective anticoagulation with LMWH. (Annotation #38)
6. Arrange for home therapy in appropriate patients. (Annotation #42)

Deep Vein Thrombosis (DVT) Diagnosis Algorithm Annotations

1. Leg Symptoms/Clinical Suspicion of DVT

   As part of the evaluation, determine the history of character, location, and onset duration of the patient's leg pain and swelling. Recent unilateral swelling and pain, above or below the knee, without any explanatory bone or joint trauma is suspicious for DVT.

   Determine the patient's history of previous thromboembolism, family history of VTE, if patient is currently pregnant or recently postpartum, presence of cancer, recent trauma or surgery, immobilization, presence of varicosities and current estrogen use. Long travel time or flight longer than 8 hours may also be risk factors.

   Exam findings may include erythema, warmth, and/or superficial thrombophlebitis with a palpable tender cord over a superficial vein. In the most severe form, plegmasia cerulia dolens, the venous drainage of the lower extremity is acutely and severely obstructed threatening limb viability. This may require other treatment (see Annotation #47, "Other Therapies.")

   It is well known that clinical findings are poor predictors of the presence or severity of thrombosis. Therefore, determining Pretest Probability is necessary in managing the diagnostic process (see Annotation #2, "Determine Pretest Probability.")

   The work group feels that patients who also have signs and symptoms of pulmonary embolism should be evaluated according to the PE Diagnosis Algorithm. Please refer to Annotation #14, "Clinical Signs and Symptoms of PE."

   Evidence supporting this recommendation is of classes: D, R

2. Determine Pretest Probability

   The work group recommends the use of a formal protocol to determine a patient's pretest probability of DVT. This can guide the appropriate choice of test(s) and follow-up necessary to safely triage patients for this condition, which can produce minimal signs and symptoms but lead to serious consequences if left untreated. Please refer to Annotation Appendix A, "Well's Model of the Clinical Pretest Probability of DVT" in the original guideline document for an example of a clinical pretest probability model (protocol).

   Evidence supporting this recommendation is of classes: A, B, C, M

3. Low Pretest Probability

   Patients with a low pretest probability of DVT (such as those with a score of zero on Well's scoring) can safely be managed by obtaining a D-dimer assay before ordering a compression ultrasound of the leg. If the D-dimer is negative, ultrasound can be omitted, and repeat ultrasound in one week is not necessary (as previously recommended in earlier versions of this

guideline). If D-dimer assays are not available to the practitioner, patients should be directed to ultrasound.

Evidence supporting this recommendation is of classes: B, D

4. D-dimer?

   D-dimer assays have been proven to have a strong negative predictive value for patients with a low pretest probability of DVT. Many D-dimer assays are available, however, they are not all equivalent. Enzyme linked immunoassay (ELISA), rapid ELISA (VIDAS®), and SimpliRED® assays have been proven to have a strong negative predictive value. In general, D-dimer testing is most appropriate for use in ambulatory care settings for patients with recent onset of symptoms who are not currently on anticoagulation therapy. D-dimer assays have a low specificity; therefore, a positive assay alone should not be used to make an affirmative diagnosis of DVT. A positive D-dimer assay in a patient with low pretest probability of DVT should be followed by a compression ultrasound to confirm the diagnosis. If D-dimer assays are not available to the practitioner, patients with a low pretest probability should be directed to ultrasound. For patients with suspected DVT, D-dimer testing, done correctly, has the potential to significantly decrease the need for initial and subsequent radiological investigation. [Conclusion Grade II: See Conclusion Grading Worksheet – Appendix A – Annotations #4 and 11 (DVT D-dimer)]

   Evidence supporting this recommendation is of classes: B, C, M, R

5. DVT Excluded - Out of Guideline

   Patients with a low pretest probability of DVT and a negative (reliable) D-dimer assay have a very low (<2%) risk of subsequent finding of DVT. These patients can be followed clinically with no further radiologic evaluation unless warranted by new or progressive clinical symptoms.

6. Venous Ultrasound?

   Patients with a low pretest probability of DVT and a positive D-dimer assay should receive an ultrasound to confirm the diagnosis of DVT. The ability to diagnose DVT may vary depending on the proximity of the suspected DVT site. In addition, the interpretation of the venous ultrasound can be difficult in patients with a previous history of DVT. Consider consulting with the interpreting physician. (See Discussion and References #13, "Follow-Up Studies/Second Venous Ultrasound or Venography" in the original guideline document.)

   Evidence supporting this recommendation is of classes: A, C, R

7. DVT Confirmed - See Venous Thromboembolism (VTE) Treatment Algorithm

   Proximal Thrombosis (at or above the popliteal vein)

Proximal thrombosis should be treated with anticoagulation unless contraindicated. (See Annotation #37, "Complicated VTE or Comorbidities?") Additional information can also be found in the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) Anticoagulation Therapy Supplement.

Calf Thrombosis (below the popliteal vein)

Increasing evidence suggests that patients with symptomatic calf DVT benefit from treatment similar to that for proximal DVT. If not treated, these patients should be followed by serial compression ultrasounds to rule out proximal progression of thrombus to popliteal vein.

Evidence supporting this recommendation is of classes: A, C, D, R

8. Moderate/High Pretest Probability

   Patients with moderate or high pretest probability have a 15 to 70% risk of DVT. Because of the high incidence of DVT in this population, venous Doppler ultrasound should be ordered as the first test, and D-dimer assay can be used after a negative ultrasound result to determine further radiologic testing needs.

9. Venous Ultrasound?

   Patients with a moderate/high pretest probability of DVT should receive a compression ultrasound as the first test to diagnose DVT. A negative result on the venous ultrasound can be followed by D-dimer to determine further radiologic testing needs. A positive result on the ultrasound confirms the diagnosis of DVT.

   Evidence supporting this recommendation is of classes: B, C

10. DVT Confirmed -- See Venous Thromboembolism (VTE) Treatment

    Please refer to Annotation #7, "DVT Confirmed - see Treatment Algorithm," and the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information.

11. D-dimer?

    It has been found safe to withhold anticoagulation among outpatients with a low clinical suspicion, a negative ultrasound, and a negative D-dimer.

    For patients with suspected DVT, D-dimer testing, done correctly, has the potential to significantly decrease the need for initial and subsequent radiological investigation. [Conclusion Grade II: See Conclusion Grading Worksheet -- Appendix A -- Annotations #4 and #11 (DVT D-dimer) in the original guideline document.]

    Evidence supporting this recommendation is of classes: B, C

13. Follow-Up Studies/Second Venous Ultrasound (3-7 Days) or Venography

    Clinical pretest probability, D-dimer, and venous Doppler ultrasound are adequate to rule in or rule out DVT in the majority of cases. If DVT is strongly suspected despite a negative initial ultrasound, consider venography or repeat ultrasound in 3 to 7 days. Please refer to Annotation Appendix A, "Model of the Clinical Pretest Probability of DVT," in the original guideline document.

    The combined use of clinical pretest probability, D-dimer, and ultrasound is effective in confirming or excluding the diagnosis of DVT in the majority of cases. If clinical suspicion of DVT is high and ultrasound is negative, consider further testing, such as repeat ultrasound for suspected calf thrombosis or venography for suspected proximal thrombosis. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix B -- Annotations #7 and 10 (DVT Diagnosis Confirmation) in the original guideline document.]

    A. Serial ultrasonography

       When calf thrombosis is suspected but the initial ultrasound is negative, serial ultrasound is an acceptable alternative to venography. If a thrombus were discovered, anticoagulation would be recommended.

    B. Computed tomography (CT) venography of the inferior vena cava and the iliac veins is performed at some institutions to visualize proximal obstructions. The common, superficial and deep femoral veins can be done as well. CT venography does not include the distal calf veins.
    C. Contrast venography (proximal, intra-abdominal)
    D. Magnetic Resonance Imaging (MRI) - experimental

    Evidence supporting this recommendation is of classes: A, C, R

Pulmonary Embolism (PE) Diagnosis Algorithm Annotations

14. Clinical Signs and Symptoms of PE

    Pulmonary embolism (PE) should be considered in patients that present with the three most frequent signs and symptoms: dyspnea, pleuritic chest pain, and tachypnea. Less frequent signs/symptoms are cough, hemoptysis, fever, syncope, diaphoresis, nonpleuritic chest pain, apprehension, rales, wheezing, hypotension, tachycardia, cyanosis, or pleural rub. Clinical findings are nonspecific and should not be used as the only criteria to diagnose PE.

    Evidence supporting this recommendation is of classes: C, R

15. Estimate Clinical Pretest Probability

    If high risk, begin LMWH without delay

    Patients presenting with signs and symptoms of pulmonary embolism need:

- Complete history and physical exam
- Risk factor assessment (pretest probability). If high-risk, begin heparin promptly (a tool for determining pretest probability is shown in annotation Appendix B, "Model for Predicting Clinical Pretest Probability of PE" in the original guideline document).
- Chest x-ray (CXR), arterial blood gasses (ABG's), electrocardiogram (EKG) and other tests as indicated for alternative diagnoses considered
- Patients who present signs and symptoms of massive PE (syncope, hypotension, tachycardia, and hypoxia) may require evaluation and treatment different than that recommended in this guideline. In patients with suspected massive PE, echocardiography can be used as a diagnostic and management tool. Please refer to Annotation #37, "Complicated Venous Thromboembolism or Comorbidities" in the Venous Thromboembolism Treatment Algorithm.

Evidence supporting this recommendation is of classes: B, C, R

16. Choose Lung Imaging Study

Current practice is to choose between two methods to image the pulmonary blood vessels:

A. Helical CT pulmonary angiography
B. Ventilation/perfusion (V/Q)scan

The choice of initial imaging study depends on several factors, including how readily available the tests are, the resolution of images obtained, underlying illnesses of the patient, and experience of the radiologists.

Evidence supporting this recommendation is of classes: C, R

17. Ventilation/Perfusion (V/Q) Lung Scan

In many centers a ventilation/perfusion (V/Q) scan is considered the initial test when the chest x-ray is normal and the patient does not have underlying heart disease or chronic obstructive pulmonary disease (COPD)/asthma. This will increase the chances of getting an interpretation that is diagnostic. In general, normal and high probability scans are considered diagnostic unless the clinical probability strongly suggests otherwise. Low, intermediate, and indeterminate readings are considered non-diagnostic and have a probability of PE that ranges from about 15 to 40%. Further testing is usually required. When a contrast load needs to be avoided, such as in patients with renal insufficiency or dye allergy, the V/Q scan is preferred.

New studies suggest that helical CT is as sensitive and specific, if not more so, than V/Q scanning for both diagnostic and non-diagnostic exams. In the proper clinical setting (no renal failure and technical expertise in helical CT scanning for PE) CT may be the preferred modality in all patients. Please see the ICSI Technology Assessment Report, Contrast-Enhanced Helical Computed Tomography for the Diagnosis of Pulmonary Embolism.

Evidence supporting this recommendation is of classes: B, C, R

18. V/Q Normal

A normal perfusion scan, irrespective of ventilation abnormalities, essentially excludes the diagnosis of PE.

Evidence supporting this recommendation is of classes: D, R

19. Follow-Up Other Diagnosis

Patients who have had PE excluded as the likely diagnosis should be followed-up clinically to evaluate and treat alternative causes for the symptoms.

Other clinically important disorders such as pericarditis, myocardial infarction, and pneumonia should be excluded in the appropriate circumstances. In patients for whom spiral CT is used to determine the presence of PE, alternative diagnosis may be evident without additional testing.

20. V/Q Non-Diagnostic (Low or Intermediate)

Intermediate probability and low probability (non-diagnostic)V/Q lung scans are determined by radiologic criteria. Unfortunately, it has been shown that patients who fit into this "non-diagnostic" category have an incidence of pulmonary embolism that varies from 15 to 40%. Further diagnostic studies are recommended in patients with non-diagnostic ventilation perfusion scans.

Evidence supporting this recommendation is of class: C

21. V/Q Diagnostic (High Probability)

The significance of a high probability diagnostic V/Q scan depends on the clinical pretest probability of PE. Several clinical studies have demonstrated that high probability scans are associated with PE at least 85% of the time. If the clinical suspicion is intermediate or high, this test can be considered a final diagnostic test. However, if the clinical suspicion is actually low, the incidence of pulmonary embolism appears to be 35 to 55%. In this circumstance, one should consider further evaluation with a CT pulmonary angiogram. A positive CT pulmonary angiogram in central pulmonary arteries has a high degree of specificity and may be considered diagnostic. A positive CT pulmonary angiogram in peripheral vessels may not represent a true positive finding. Depending upon the pretest probability, the patient may need further work-up with a standard pulmonary angiogram.

Evidence supporting this recommendation is of classes: B, R

22. Clinical Pretest Probability

In patients with low clinical pretest probability, the lung scan is frequently false positive. Two studies have demonstrated 45 to 66% of high probability

(diagnostic) V/Q scans were falsely positive in this situation, and further testing with angiography is indicated.

In patients with intermediate or high clinical pretest probability, a high probability (diagnostic) V/Q scan has 85 to 90% sensitivity for PE and can be considered the confirmatory test. Proceed to the Venous Thromboembolism (VTE) Treatment Algorithm.

Evidence supporting this recommendation is of class: B

24. Angiogram Positive?

Pulmonary angiography is considered the diagnostic reference standard for the diagnosis of PE and is indicated when there is significant doubt about a diagnosis of PE after non-invasive studies. It is often performed when lung scan results are non-diagnostic or when the results are at odds with the clinical impression. An angiogram is generally safe and well-tolerated in selected patients. Benefits outweigh the risks when a definitive diagnosis is necessary.

Evidence supporting this recommendation is of classes: B, C, D

25. Diagnosis PE

Patients with a high probability (diagnostic) V/Q scan and intermediate or high clinical pretest probability are essentially confirmed positive for PE. They can be considered for treatment with no further diagnostic testing.

Evidence supporting this recommendation is of classes: B, C, R

26. CT Pulmonary Angiography Positive?

CT pulmonary angiography (high speed thin collimation spiral/helical CT or electron beam CT) provide an excellent alternative in patients with abnormal chest x-rays. CT pulmonary angiography is also more useful in patients with underlying cardiac disease and COPD/asthma. When alternative diagnoses are likely, CT pulmonary angiography is especially good as it can rule out PE and confirm other diagnoses with one test. CT pulmonary angiography may be the initial test if the hospital has state of the art equipment and technical and interpretive expertise. Consultation with a radiologist may be helpful in determining the most appropriate test.

CT pulmonary angiography has a high sensitivity and specificity for central clots. The sensitivity and specificity drop substantially for peripheral clots. With state of the art equipment the ability to exclude peripheral clots is probably increasing but the clinical probability must guide the decision to pursue further testing (compression ultrasound or pulmonary angiography).

Evidence supporting this recommendation is of classes: M, R

27. Compression Ultrasound of Lower Extremities

In patients with non-diagnostic V/Q scans and negative CT pulmonary angiography results, further evaluation with compression ultrasound can be used to improve clinical likelihood of disease and avoid more invasive testing. Please refer to Annotation Appendix C in the original guideline document for sample compression ultrasound orders.

Evidence supporting this recommendation is of classes: C, D, M

28. Compression Ultrasound Positive?

29. Diagnosis VTE

A positive ultrasound usually confirms the diagnosis of DVT and requires treatment regardless of the presence or absence of PE. If the ultrasound is negative, further evaluation may be warranted, dependent upon the patient's clinical pretest probability.

30. Low Clinical Pretest Probability

Patients with a non-diagnostic V/Q scan or negative CT pulmonary angiography associated with a negative compression ultrasound and low clinical pretest probability have a low incidence of PE. It is safe to withhold anticoagulation therapy and follow these patients clinically. Please refer to Annotation #35, "Follow-Up"

Evidence supporting this recommendation is of classes: B, C, R

31. Intermediate Clinical Pretest Probability

Patients with a non-diagnostic V/Q scan or negative CT pulmonary angiography associated with a negative compression ultrasound, but with intermediate clinical pretest probability, have a small but significant incidence of PE.

Follow-up studies such as D-dimer testing or serial compression ultrasounds are recommended to improve the diagnostic sensitivity for PE while avoiding invasive diagnostic tests. Please refer to Annotation #34, "D-dimer or Serial Ultrasound".

Evidence supporting this recommendation is of classes: B, C, R

32. High Clinical Pretest Probability

A significant incidence of PE is found in patients with non-diagnostic V/Q scan or negative CT pulmonary angiography associated with a negative compression ultrasound, but a high clinical pretest probability. Pulmonary angiography is recommended in this subgroup. Please refer to Annotation #24, "Angiogram Positive?"

Evidence supporting this recommendation is of classes: B, C, R

34. D-dimer or Serial Ultrasound

It is safe to withhold anticoagulation among outpatients with a low clinical suspicion of acute PE, an intermediate probability (non-diagnostic) lung scan, and a negative D-dimer (ELISA or automated luminescence immunoassay [LIA]). The assay-specific D-dimer cutoff value must provide a high sensitivity (e.g., greater than or equal to 95%) in order for the D-dimer to be used as outlined above.

The risks associated with a misdiagnosis of PE are typically more severe than those associated with a misdiagnosis of DVT. Higher negative predictive values are required to safely use D-dimer to exclude PE. The evidence, to date, suggests that current assays, with the possible exception of ELISA and rapid ELISA methods, are not acceptable for use in excluding PE in patients with clinical suspicion of PE. [Conclusion Grade III: See Conclusion Grading Worksheet -- Appendix C --Annotations #34 (PE D-dimer) in the original guideline document]

If the patient has an intermediate clinical pretest probability for DVT and the initial compression ultrasound was negative, but DVT is still strongly suspected, consider a repeat ultrasound in 3 to 7 days.

Evidence supporting this recommendation is of classes: B, C, M, R

35. Follow-Up

The incidence of PE is low in patients with low clinical pretest probability and negative or non-diagnostic studies. Alternative diagnoses should be considered and clinical follow-up is recommended.

Evidence supporting this recommendation is of classes: B, C, R

Venous Thromboembolism (VTE) Treatment Algorithm Annotations

37. Complicated Venous Thromboembolism or Comorbidities?

Patients with complicated venous thromboembolism or certain comorbidities may require therapy that is different than patients with uncomplicated venous thromboembolism. The work group felt that these patients should be identified and treated individually rather than by a standard guideline.

Massive PE

Patients who present with symptoms of PE associated with hemodynamic or respiratory compromise should be evaluated for massive PE. These patients may require treatment other than that discussed in the guideline.

Patients with hemodynamic compromise may require immediate thrombolytic therapy. Normotensive PE patients with right ventricle (RV) dysfunction should be treated in-hospital (at least initially) where their vital signs can be closely monitored. Such patients should be considered for thrombectomy

(either catheter-directed or open), thrombolysis, and/or inferior vena cava (IVC) filter placement if blood pressure support (i.e., pressors and augmentation of intravascular volume) is required, and possibly if hypoxemia cannot be corrected with supplemental oxygen therapy.

Evidence supporting this recommendation is of classes: A, B, D, M, R

Contraindications to Anticoagulation

Absolute contraindications would include patients who have active severe hemorrhage or recent intracranial hemorrhage. Relative contraindications include: recent or imminent surgery, trauma, anemia (hematocrit less than 30), renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease, and liver disease.

These patients require more intense monitoring for bleeding complications if given anticoagulation therapy, serial ultrasounds for untreated calf DVT, or IVC filters for proximal DVT if not treated with anticoagulation therapy. (See Annotation #47, "Other Therapies".) Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on contraindications to anticoagulation.

Evidence supporting this recommendation is of classes: A, B

Known History of Heparin Induced Thrombocytopenia (HIT)

Patients with HIT should not be treated with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Direct thrombin inhibitors have been used successfully in this circumstance. (See Annotation #47, "Other Therapies".) Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on HIT.

Evidence supporting this recommendation is of class: C

Extensive Iliofemoral Thrombosis/Phlegmasia

Patients found to have extensive iliofemoral disease or evidence of phlegmasia will likely require inpatient monitoring and longer course of heparin/LMWH therapy than patients with uncomplicated DVT. Thrombolytic therapy may be of benefit in these patients for possible reduction of post-thrombotic complications. (See Annotation #47, "Other Therapies".)

Pregnancy

In pregnancy, warfarin (Coumadin®) is contraindicated because it crosses the placenta and is associated with embryopathy, central nervous system (CNS) abnormalities, and neonatal bleeding. Subcutaneous UFH, twice daily, has been the standard therapy in pregnancy. LMWH has shown no increased fetal complication, and was shown to have fewer bleeding complications than UFH. Anticoagulation will need to continue 4 to 6 weeks after delivery because the postpartum period is itself a high-risk time for thrombosis.

Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on anticoagulation therapy during pregnancy.

Evidence supporting this recommendation is of classes: A, D, M

Familial Bleeding and Clotting Disorders

Patients with certain disorders should be treated individually as length of therapy, warfarin dosing, and target international normalized ratio (INR) can be different depending upon the particular condition. These patients are excluded from the guideline.

Severe Renal Dysfunction (creatinine clearance less than 30 mL/minute)

These patients require closer monitoring for bleeding complications and dosing adjustments if LMWH is used. Patients with significant renal impairment (creatinine clearance less than 30 mL/min) can accumulate LMWH. The recommended doses in these patients are now:

- Enoxaprain (Lovenox®) 1 mg/kg ONCE daily for therapeutic (treatment) doses. (Normal renal function dose is 1 mg/kg twice daily or 1.5 mg/kg once daily)
- Enoxaprain (Lovenox®) 30 mg ONCE daily for prophylactic doses. (Normal renal function dose is 30 mg twice daily or 40 mg once daily)

Please refer to the NGC summary of ICSI's ICSI Anticoagulation Therapy Supplement for more information on anticoagulation therapy in patients with renal dysfunction.

Evidence supporting this recommendation is of classes: B, C

38. Low Molecular Weight Heparin (LMWH)/Unfractionated Heparin (UFH)

It is safe to withhold anticoagulation among outpatients with a low clinical suspicion of acute PE, an intermediate probability (non-diagnostic) lung scan, and a negative D-dimer (ELISA or automated luminescence immunoassay). The assay specific D-dimer cutoff value must provide a high sensitivity (i.e., greater than or equal to 95%) in order for the D-dimer to be used as outlined above.

UFH or LMWH should be considered for the initial treatment of PE. LMWH is the preferred heparin for the initial anticoagulation of patients with DVT. It is as safe and as effective as continuous UFH. Suitable patients can be safely treated with LMWH in the outpatient setting. [Conclusion Grade I: See Conclusion Grading Worksheet -- Appendix D -- Annotation #38 (Low Molecular Weight Heparin) in the original guideline document]

Heparin should be continued for at least 5 days after the initiation of warfarin therapy and until INR is above 2.0 for two consecutive days.

Low Molecular Weight Heparin (LMWH)

Low molecular weight heparins provide reliable anticoagulation levels when given subcutaneously on a weight-determined dosing schedule. No laboratory monitoring of the intensity of anticoagulation is required for LMWH, except for special circumstances. Please note LMWH may not be appropriate for patients with renal insufficiency (creatinine clearance less than 30 mL/min). (See Annotation #37, "Complicated Venous Thromboembolism or Comorbidities?")

- Enoxaparin (Lovenox®) 1.5 mg/kg subcutaneously (SQ) once daily (qD) (Food and Drug Administration [FDA] approved for inpatient venous thromboembolism treatment). Enoxaparin 1.5 mg/kg SQ once daily is an option for patients with uncomplicated DVT. For uncomplicated patients, once daily dosing is as effective and safe as twice daily dosing, is more convenient, and reduces the cost of enoxaparin therapy. Risk factors with once daily dosing include obesity (greater than 100 kg), cancer, and chronic kidney disease. Twice daily dosing (enoxaparin 1mg/kg SQ twice daily [BID]) is recommended for obese patients and patients with cancer.
- Tinzaparin (Innohep®) 175 anti-Xa IU/kg SQ qD (FDA approved for venous thromboembolism treatment)
- Dalteparin (Fragmin®) 100 IU/kg SQ BID (not FDA approved for venous thromboembolism treatment)
- Dalteparin (Fragmin®) 200 IU/kg SQ qD (The effectiveness of once daily dosing is controversial) (not FDA approved for venous thromboembolism treatment)

The decision for hospital or home therapy is not mutually exclusive. A patient could be started on LMWH in the hospital and discharged to continue therapy at home at any time during the course of therapy.

Evidence supporting this recommendation is of classes: A, B, C, M, R

Unfractionated Heparin (UFH)

UFH is administered by continuous intravenous (IV) infusion following a bolus dose.

Evidence supporting this recommendation is of classes: A, C, R

Heparin-Induced Thrombocytopenia (HIT)

Both UFH and LMWH are associated with heparin-induced thrombocytopenia (HIT). Monitoring should include a baseline platelet count and periodic platelet counts during heparin therapy. Heparin therapy should be discontinued if the platelet count drops by more than 50% from baseline labs or below 100,000 mm^3.

Heparin alternatives can be considered for patients with a heparin allergy. Fondaparinux (Arixtra) is a synthetic pentasaccharide that inhibits Factor X. It is FDA approved only for prophylactic use, but treatment is supported by a recent study.

- Arixtra 5mg SQ once daily (for patients less than 50 kg)
  7.5 mg SQ once daily (if 50-100 kg)
  10 mg SQ once daily (if greater than 100 kg)

Duration is similar to the LMWH – Arixtra should be continued for at least 5 days, and until the INR has been greater than 2 for two consecutive days. Studies have excluded patients with active bleeding, thrombocytopenia (a platelet count below 100,000 mm^3), and pregnancy. Arixtra is contraindicated in patients with active bleeding, thrombocytopenia, severe renal impairment (creatinine clearance less than 30 mL/min), and in patients with a body weight less than 50 kg. Warnings include moderate renal impairment (creatinine clearance 30 to 50 mL/min), elderly (greater than 75 years of age), uncontrolled hypertension, and spinal puncture. Laboratory monitoring of the intensity of anticoagulation is generally not needed. Arixtra side effects include bleeding, thrombocytopenia, and increases in serum aminotransferases. There is no antidote to reverse the effects of Arixtra. Other heparin alternatives are lepirudin (Refludan), argatroban (Argatroban), and bivalirudin (Angiomax).

Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on low molecular weight and unfractionated heparins, synthetic pentasaccharides, and HIT.

Evidence supporting this recommendation is of class: A

39. Warfarin

It is recommended that warfarin therapy be initiated with a dose of 5 mg (less in patients with risks for increased sensitivity to warfarin) with dosage adjustments based on results of INR testing.

1. A high-loading dose of warfarin (greater than 10 mg) is of no clinical use and should be discouraged.
2. A 10 mg initial dose of warfarin has been associated with early over-anticoagulation and, when compared to a 5 mg initial dose, was no more effective in achieving a therapeutic INR by day 4 or 5 of therapy.

A therapeutic range of anticoagulation to keep the INR at 2.5 (range 2.0 to 3.0) is recommended for patients with VTE.

The ICSI Anticoagulation Therapy Supplement contains additional information on warfarin therapy including an appendix on interactions with warfarin.

Evidence supporting this recommendation is of classes: A, B, D, R

40. Outpatient Treatment Appropriate?

Medical criteria for safe outpatient therapy include:

- Uncomplicated venous thromboembolism. (See Annotation #37, "Complicated Venous Thromboembolism or Comorbidities?")
- Good cardiorespiratory reserve
- No excessive bleeding risks
- Creatinine clearance greater than 30 mL/minute. (creat $\geq$2 mg/dL)

Because of decreased cardiorespiratory reserve, patients presenting with symptomatic PE should initially be treated in-hospital.

Other considerations include:

- Patients need to be taught how to administer the drug and recognize complications.
- Daily INRs will be needed to guide the institution of warfarin therapy. The warfarin dose will need to be adjusted to the INR.
- Patients will need resources to answer questions and deal with problems.

Evidence supporting this recommendation is of classes: A, C, D

41. Inpatient Treatment

Therapy is discussed in Annotation #38, "Low Molecular Weigh Heparin (LMWH)/Unfractionated Heparin (UFH)" and in Annotation #39, "Warfarin".

42. Outpatient Protocol

Because of the need for an organized support system and time of day considerations for home care agencies, many patients may need hospitalization during the first 24 hours to start therapy promptly.

A. All stable VTE patients
    - Daily LMWH shots self administered, caregiver administered, or daily clinic visits. The patient will need to be geographically accessible to have INRs drawn and receive care for problems that arise.
    - Daily INR for transitioning to warfarin treatment after 2 days of adequate anticoagulation. (For details see Anticoagulation Therapy Supplement)
    - Duration of anticoagulation to be determined by the supervising physician.

B. DVT patients
    - If the criteria in Annotation #40 can be met, DVT treatment can be started in the outpatient setting; otherwise hospitalize until teaching, medication and close follow-up can be assured.
    - For DVT use graduated compression stockings on the affected leg to reduce the risk of postphlebitic syndrome.

- Compression combined with early ambulation does not cause any increase in pulmonary embolism and gives more rapid resolution of pain and swelling.

Evidence supporting this recommendation is of classes: A, D

43. Patient Education

Patients should be instructed on the use of anticoagulation. Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on patient education.

44. Complications During Therapy?

Patients with complicated venous thromboembolism or certain comorbidities may require therapy that is different than patients with uncomplicated venous thromboembolism. These patients should be identified and treated individually rather than by a standard guideline.

Patients on UFH or LMWH therapy who have bleeding, thrombocytopenia, or osteoporosis may require individual adjustments in therapy. HIT should be suspected if the platelet count is less than 100,000 mm^3 or the count drops 50% or more from baseline labs.

Patients on warfarin therapy who experience bleeding, skin necrosis, or who become pregnant may require individual adjustments in therapy.

The development of a complication attributable to anticoagulation requires action by the health care team. Sometimes, as with heparin-induced thrombocytopenia, the drug must be discontinued. The most common complication, bleeding, may require a dosage adjustment, discontinuation of the drug, or further evaluation in the setting of gastrointestinal or genitourinary bleeding. Specific actions are best determined in a case-by-case basis by the clinician, who can appropriately weigh the risks and benefits of continued anticoagulation therapy and who can take into account the timing of the complication.

Please refer to the NGC summary of ICSI's Anticoagulation Therapy Supplement for more information on potential complications of anticoagulation therapy.

45. Anticoagulation Failure?

Recurrent symptomatic DVT or PE during adequate heparin or warfarin treatment represents failure of treatment and needs objective documentation, especially as a new DVT may be difficult to distinguish from postphlebitic syndrome. In certain circumstances, alternate treatment such as an inferior vena cava filter may be indicated. If a patient fails on warfarin therapy, heparin or LMWH may need to be reinstituted. The work group felt these patients should be identified and treated individually rather than by a standard guideline.

46. Continued Anticoagulation With Follow-Up and Secondary Prevention

General Follow-Up Considerations

A. Duration of Anticoagulation

Duration of anticoagulation should be individualized to the patient. General consensus points of the American College of Chest Physicians (ACCP) include:

1. Transient risk (e.g., surgery, immobilization, estrogen use, trauma): 3 to 6 months
2. Idiopathic or medical risk: 6 to 12 months, and
3. Recurrent disease or continued risk factors: indefinite

[Conclusion Grade II: See Conclusion Grading Worksheet -- Appendix E -- Annotation #46 (Duration of Anticoagulation) in the original guideline document]

Evidence supporting this recommendation is of classes: A, B, R

B. Anticoagulation Management

A coordinated effort for follow-up of patients started on warfarin is required to minimize the risks of both hemorrhagic and thrombotic complications while on treatment. In the first several weeks of anticoagulation, INRs need to be checked at least weekly. After stabilization, the interval between INRs can be increased from weekly to biweekly, up to but not beyond 4 weeks.

A goal INR target of 2.5 is recommended for the majority of patients who are kept on long-term anticoagulation. Patients who have recurrent VTE on adequate anticoagulation with coumadin may require a higher target INR (e.g. 3.0). One study suggested protection against recurrence in patients who were initially treated for 6 months at the target INR of 2.5, then treated to an INR range of 1.5 to 2.0. However, a recent study comparing long-term anticoagulation either at INR 2.5 versus INR 1.5 to 2.0 showed greater protection against recurrence with the higher target INR of 2.5.

Supporting evidence is of classes: A, C, R

C. Long-Term Complications

Long-term complications for patients treated for DVT include recurrent VTE, postphlebitic syndrome, and bleeding while on anticoagulation therapy. Postphlebitic syndrome is characterized by symptoms of heaviness of the leg, fatigue, and pain with findings of dependent edema, skin pigmentation, and venous varicosities. Patients should be counseled when discontinuing warfarin to watch for signs of recurrence and report them immediately. Ambulatory exercise programs are

unlikely to exacerbate symptoms and may result in improved leg muscle flexibility.

Evidence supporting this recommendation is of classes: C, D, R

D. Graded Compression Stockings (not Teds)

Knee-high 30 to 40 mm Hg custom fitted, graded compression stockings help alleviate symptoms of edema and pain in patients who have postphlebitic syndrome. One report showed that graded compression stockings reduced the incidence of postphlebitic syndrome by 50% in patients with acute DVT. For chronic or recurrent venous stasis ulcer, consultation with a vascular surgeon should be considered.

Evidence supporting this recommendation is of classes: A, C, D

E. Look for malignancy?

Some patients who present with idiopathic DVT may have occult malignancy. However extensive work-ups in asymptomatic patients beyond appropriate cancer screening have not shown benefit.

Evidence supporting this recommendation is of classes : B, C

F. Thrombophilia

Certain patients should be tested for thrombophilia. This testing should be done 2 weeks after discontinuation of anticoagulation. (See the original guideline document for laboratory test values prevalent in patients with DVT). The work group recommends consideration be given to a discussion with a thrombophilia expert for:

- Patients who have recurrent thromboembolic disease
- Patients with first idiopathic DVT who:
    - Are less than 50 years of age
    - Have a family history of VTE among one or more first degree relatives
    - Have an unusual site of spontaneous thrombosis
    - Have massive venous thrombosis

Evidence supporting this recommendation is of classes: B, C, D, R

G. Activity Level

There is no evidence that restriction of activity is of benefit nor is there evidence to determine the appropriate activity level. The physician needs to be guided by individual patient circumstance, including pain and swelling.

Evidence supporting this recommendation is of class: C

47. Other Therapies

Inferior Vena Cava (IVC) Filters

Accepted indications for inferior vena caval interruption include:

- Patients with PE or proximal DVT and contraindications to anticoagulation
- Progressive thromboembolism, despite adequate anticoagulation
- Patients with underlying pulmonary hypertension in whom a PE would likely be fatal.

Consultation with a specialist is strongly recommended prior to placement of a filter, as long-term sequelae of filter placement include increased risks of recurrent DVT and PE.

Evidence supporting this recommendation is of classes: A, C, R

Serial Ultrasound in Calf DVT

Serial ultrasound (e.g. at 3 and 7 days) may be useful to evaluate for propagation of thromboses in two groups of patients:

- Patients with a positive diagnosis of a calf thrombosis, but contraindications to anticoagulation therapy
- Patients with clinical suspicion of calf thrombosis, but initial negative ultrasound. In general, patients with symptomatic calf DVT who do not have contraindications to anticoagulation will do better if treated similar to those with a proximal DVT.

Evidence supporting this recommendation is of classes: A, B, C, D, R

Treatment of Heparin-Induced Thrombocytopenia (HIT)

Patients developing HIT while on heparin therapy should be taken off all UFH and LMWH. Direct thrombin inhibitors have been used to treat HIT successfully. Direct thrombin inhibitors approved for the treatment of HIT include lepirudin (Refludan®), argatroban (Acova®), and bivalirudin (Angiomax®.) Direct thrombin inhibitors must be administered by continuous IV infusion necessitating hospitalization. Direct thrombin inhibitor therapy must be monitored by measuring the activated partial thromboplastin time (aPPT).

Evidence supporting this recommendation is of class: R

Intravenous (IV) Thrombolytic Therapy

Lytic therapy has been used in patients with extensive iliofemoral disease who demonstrate evidence of vascular compromise (phlegmasia). This therapy has

been suggested as a means of reducing the incidence of post-thrombotic syndrome. However, long-term randomized studies comparing this therapy to standard anticoagulation have not been performed. Management should be individualized and is most appropriate for patients with massive iliofemoral thrombosis. Consultation with a specialist is strongly recommended prior to initiation of lytic therapy.

Thrombolytic therapy results in more rapid clot resolution, but it does not significantly reduce mortality or the risk of recurrent PE in hemodynamically stable patients. Pooled data shows thrombolytic therapy has an increased incidence of major hemorrhage and intracranial hemorrhage as compared to UFH therapy alone. Elevated diastolic blood pressure is a risk factor for intracranial hemorrhage.

Evidence supporting this recommendation is of classes: A, D, M, R

Surgical Thrombectomy

In a highly select group of patients, surgical venous thrombectomy has been utilized. These patients typically have extensive venous thrombosis and have contraindications for anticoagulation and lytic therapy. Management should be individualized. The morbidity and mortality associated with this surgical procedure deems it be a procedure of last choice.

Evidence supporting this recommendation is of class: D

Definitions:

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study

- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

CLINICAL ALGORITHM(S)

Detailed and annotated clinical algorithms are provided for:

- Deep Vein Thrombosis (DVT) Diagnosis
- Pulmonary Embolism (PE) Diagnosis
- Venous Thromboembolism (VTE) Treatment

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting each recommendation. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Prevention of progression or recurrence of thromboembolic disease
- Reduced risk of complication from anticoagulation therapy
- Reduced use of resources and reduced costs in the diagnosis and treatment of venous thromboembolism

POTENTIAL HARMS

Diagnosis

The risks associated with a misdiagnosis of pulmonary embolism (PE) are typically more severe than those associated with a misdiagnosis of deep vein thrombosis (DVT). Higher negative predictive values are required to safely use D-dimer to exclude pulmonary embolism.

Treatment

- Patients on unfractionated heparin (UFH) or low molecular weight heparin (LMWH) therapy who have bleeding, thrombocytopenia, or osteoporosis may require individual adjustments in therapy. Heparin-induced thrombocytopenia (HIT) should be suspected if the platelet count is less than 100,000 mm^3 or the count drops 50% or more from baseline labs.
- Patients on warfarin therapy who experience bleeding, skin necrosis, or who become pregnant may require individual adjustments in therapy.
- The development of a complication attributable to anticoagulation requires action by the health care team. Sometimes, as with heparin-induced thrombocytopenia, the drug must be discontinued. The most common complication, bleeding, may require a dosage adjustment, discontinuation of the drug, or further evaluation in the setting of gastrointestinal or

genitourinary bleeding. Specific actions are best determined in a case-by-case basis by the clinician, who can appropriately weigh the risks and benefits of continued anticoagulation therapy and who can take into account the timing of the complication.

- A heparin alternative, fondaparinux (Arixtra), has side effects that include bleeding, thrombocytopenia, and increases in serum aminotransferases. There are no antidotes to reverse the effects of Arixtra.
- Refer to the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) Anticoagulation Therapy Supplement for more information on potential complications of anticoagulation therapy.

Long-Term Complications

Long-term complications for patients treated for deep vein thrombosis include recurrent venous thromboembolism, postphlebitic syndrome, and bleeding while on anticoagulation therapy. Postphlebitic syndrome is characterized by symptoms of heaviness of the leg, fatigue and pain with findings of dependent edema, skin pigmentation and venous varicosities. Patients should be counseled when discontinuing warfarin to watch for signs of recurrence and report them immediately.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to Anticoagulation

- Absolute contraindications would include patients who have active severe hemorrhage or recent intracranial hemorrhage. Relative contraindications include: recent or imminent surgery, trauma, anemia (hematocrit less than 30), renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease, and liver disease.
- These patients require more intense monitoring for bleeding complications if given anticoagulation therapy, serial ultrasounds for untreated calf deep vein thrombosis (DVT), or inferior vena cava (IVC) filters for proximal deep vein thrombosis if not treated with anticoagulation. Please refer to the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) Anticoagulation Therapy Supplement for more information on contraindications to anticoagulation.
- Fondaparinux (Arixtra) is contraindicated in patients with active bleeding, thrombocytopenia, severe renal impairment (creatinine clearance less than 30 mL/min), and in patients with a body weight less than 50 kg.

Known History of Heparin Induced Thrombocytopenia (HIT)

Patients with heparin induced thrombocytopenia should not be treated with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Direct thrombin inhibitors have been used successfully in this circumstance. Please refer to the NGC summary of the ICSI Anticoagulation Therapy Supplement for more information on heparin induced thrombocytopenia.

Pregnancy

In pregnancy, warfarin (Coumadin®) is contraindicated because it crosses the placenta and is associated with embryopathy, central nervous system (CNS) abnormalities, and neonatal bleeding. Subcutaneous UFH, twice daily, has been the standard therapy in pregnancy. Low molecular weight heparin has shown no increased fetal complication, and was shown to have fewer bleeding complications than unfractionated heparin. Anticoagulation will need to continue 4 to 6 weeks after delivery because the postpartum period is itself a high-risk time for thrombosis.

Please refer to the NGC summary of the ICSI Anticoagulation Therapy Supplement for more information on anticoagulation therapy during pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented in the original guideline document to help close the gap between clinical practice and the guideline

recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

RELATED NQMC MEASURES

- Venous thromboembolism (VTE): percentage of patients with VTE who meet the criteria for low-molecular-weight heparin (LMWH) and for whom LMWH is used.
- Venous thromboembolism (VTE): percentage of low-molecular-weight heparin (LMWH)-eligible patients with deep vein thrombosis (DVT) treated in an outpatient setting.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Venous thromboembolism. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004 Feb. 92 p. [254 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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1998 Jun (revised 2004 Feb)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health

System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT SpecialtyCare, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, Hamm Clinic, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hennepin Faculty Associates, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Health Care, North Suburban Family Physicians, NorthPoint Health &: Wellness Center, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, St. Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Winona Health

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GUIDELINE COMMITTEE

Cardiovascular Steering Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or

services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline. Readers of the guideline may assume that only work group members listed below have potential conflict of interest to disclose.

Bruce Burnett, MD is a member of the speakers bureau for Aventis, BMS, and Astra Zeneca; a consultant for Aventis, Astra Zeneca, and Sauiflo-organor; receives grant support from Aventis and BMC; and receives research support from Astra Zeneca.

No other work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Venous thromboembolism. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Apr. 93 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Anticoagulation therapy supplement. Bloomington (MN): Institute For Clinical Systems Improvement (ICSI); 2003 Nov. 54 p. See the National Guideline Clearinghouse (NGC) summary.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on February 15, 2000. The information was verified by the guideline developer on March 15, 2000. This summary was updated by ECRI on December 14, 2001 and verified by the guideline developer on January 9, 2002. The summary was updated by ECRI on January 28, 2004 and July 28, 2004.

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